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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
12/22/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/804,950	KONRADI ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 39-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,39-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed 10/14/2010.

2. Claims 1-2 and 39-41 are pending. Claims 3-38 are cancelled.

3. The following rejections are reiterated or newly applied as necessitated by amendments. Response to arguments follows.

4. This action is Final.

Withdrawn Rejections

5. The amendments of Claim 2 are sufficient to withdrawn the portion of the 35 USC 112/2nd made in section 7 with regard to parentheses. However, the rejection of Claims 1-2 and 39-41 under 35 USC 112/2nd in view of the indefiniteness of the phrase "a microarray consisting of nucleic acid molecules" is maintained. Response to arguments follows the reiterated rejection.

Newly Applied- Claim Rejections - 35 USC § 112/New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The following rejection is newly applied as necessitated by amendment.

Claims 1-2 and 39-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s),

at the time the application was filed, had possession of the claimed invention.

Upon review of the specification, the specification does not appear to provide support for the recitation of "wild-type" in Claim 1 line 3.

In response to the amendments, the reply asserts that this term means "not mutant sequences" and that support is found on p. 25 lines 11-13. The instant specification does not define the term wild type nor does the specification use the term in the specification. The description in the specification on p. 25 lines 11-13 is drawn to altered sequences relative to the sequences present in a human genome database. It appears that based upon the arguments in the amendment the applicant is equating the term "wild type" for the term "non-mutant". However, the term wild type can have meanings besides "non mutant". In particular, the definition of wild type in the art (wild type definition www.biology-online.org/dictionary) provides meaning of the term "wild type": (1) The typical (or the most common) form, appearance or strain existing in the wild. This common form of the gene is not necessarily the same as the "correct sequence in the human genome database" or a "non-mutant" as is described in the specification on p. 25. Therefore based upon the definition in the art and the lack of clear description of the term "wild type" in the specification it appears that the term would encompass new matter in the claims.

For example, the claims would include microarrays with nucleic acid molecules of ATP synthase, mitochondrial F0 complex, subunit c, isoform 3 (Claim 2). The specification describes this nucleic acid molecule as being provided by GenBank Accession number U09813 (p. 38). A review of the

GenBank Accession number indicates that there has been revisions in the nucleic structure associated with this gene (see print out U09813 Revision history and U09813 Sequence comparison www.ncbi.nlm.nih.gov). Therefore the human genome database (e.g. NCBI database) does not indicate which of these structures would be considered the "wild type" or rather which is "the typical (or the most common) form, appearance or strain existing in the wild".

These amendments to the claims, therefore, constitute new matter.

Reiterated Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-2 and 39-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2 and 39-41 are indefinite. Claim 1 is drawn to a microarray "consisting of nucleic acid molecules". This phrase is indefinite because it requires the microarray to be limited to nucleic acid molecules without any solid support. It is not clear what structure would be encompassed by a microarray consisting only of nucleic acid molecules. It is suggested that the claim be amended to reflect that the nucleic acid set on the microarray consists of a particular genetic composition and not the microarray itself in order to encompass nucleic acids on a solid support.

Response to arguments

The reply traverses the rejection. A summary of the arguments made in the reply is provided below with response to arguments following.

The applicant asserts that claim 1 previously recited a solid support, but it was deleted based upon the office's suggestion (p. 4 last paragraph to p. 5 1st paragraph). The reply asserts that in addition the definition of "microarray" indicates that a microarray includes nucleic acids molecules affixed to a solid support (p. 5 1st paragraph). The reply asserts that therefore the term "microarray" necessarily includes a solid support and therefore it is unnecessary to recite it in the claim (p. 5 1st paragraph).

These arguments have been fully reviewed but have not been found persuasive.

Although it is acknowledged that the language in claim 1 was discussed in the Interview of 3/31/2009 with regard to the art which was on the record at that time in the prosecution history. The language of the claims after further review in the previous office action filed 5/14/2010 was found indefinite and the above 35 USC 112/2nd made.

The reply points to the specification for the definition of microarray. The definition in the specification is "microarray is meant an organized collection of at least two nucleic acid molecules or polypeptides affixes to a solid support" (p. 18 lines 21-23). Consisting language is a closed language. The MPEP 2111.03 [R3] states that the transitional phrase "consisting of" excludes any element, step, or ingredient not specified in the claim. As such the term consisting

appears to be inconsistent with the definition in the specification. It is suggested that the claim be amended to e.g. "a microarray comprising probes, wherein the probes consist nucleic acid molecules...". Although this is only a suggestion of language to overcome the 35 USC 112/2nd rejection provided above, it is noted that this suggested limitation would still require that at least 90% of the probes be naturally coded for by a nuclear gene.

Reiterated Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-2 and 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Houstek et al. (Human Molecular Genetics 1999 Vol. 8 p 1967) in view of Chee et al. (WO 95/11995 May 4, 1995).

With regard to Claims 1-2, Houstek et al. teaches that mitochondrial ATPase (complex V) consists of 16 different polypeptides of which only 2 are products of mitochondrial genes whereas all other ATPase subunits are nuclear encoded (p. 1967 2nd paragraph). Houstek et al. teaches that although all mutations to date have been mtDNA mutations, that in the instant paper, a defect of ATPs was caused by altered biosynthesis of the enzyme and has a nuclear origin (p. 1967 last paragraph to p. 1968 2nd paragraph). Houstek et al. teaches that this mutation is not an mtDNA defect and suggests screening the nuclear ATPase subunits to determine the location of the mutation (p. 1971 2nd full paragraph). Houstek et al. teaches that mtDNA encoded subunits assemble at a late stage (p. 1971 last paragraph) and therefore early stage defects could be caused by nuclear genes. Therefore Houstek et al. suggests that nuclear ATPase gene defects could be responsible for early stage defects. Houstek et al. suggests that nuclear ATPase subunits should be screened. Therefore Houstek et al. suggests a reason for the skilled artisan to use a composition consisting of nuclear genes.

However, Houstek et al. does not teach a microarray consisting of 90% nuclear encoded nucleic acid fragments from complex V. The art, at the time of

filing, however, teaches that it is obvious to design microarrays to interrogate target sequences.

With regard to Claims 1-2, Chee et al teaches the design of an array comprising capture probes to make a block tiling array (see figure 16, p. 79 lines 23-39 and Figure 7, p. 37 lines 10-38). Chee et al. teaches the design of these tiling arrays to interrogate a reference sequence and its codons with a target sequence for the identification of single base mutants associated with disease (p. 11 lines 9-10 and p. 31 line 6-7). Chee et al. teaches that this design allows for simultaneous detection and quantification of multiple target sites (p. 32 lines 18-19). As such Chee et al. teaches a microarray which consists of a particular sequence that includes multiple probe sets that represent every permutation of the nucleotides for given sequence. Therefore Chee teaches a design which will allow the analysis of all combinations of nucleotides surrounding a region of interest. As such the prior art teaches that once a region of interest is determined, in this case, the nuclear ATPase subunits, that a microarray comprising every permutation of that region can be designed for the purpose of identifying mutations associated with disease.

With regard to Claims 40-41, the array designed by Chee et al. would include every permutation of the target sequences of the nuclear ATP synthase of Houstek et al. and therefore would encompass at least 25 nucleic acid molecules.

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time of filing to design a microarray consisting of nuclear ATP synthase

genes using the design constraints of Chee et al. Houstek et al. suggest screening nuclear ATP synthase genes to determine the location of a defect caused in the early stage of development. The artisan thus would have been motivated to detect mutations within the nuclear ATP synthase genes that may affect function of the genes during development. Chee et al. teaches that the design of such microarrays to screen such mutations in simultaneous fashion was known in the art. As such the ordinary artisan would have a reasonable expectation of success of designing a microarray consisting of nucleic acid probes of the nuclear ATP synthase (complex V) genes for the expressed purpose of screening for early stage defects.

Response to Arguments

The reply traverses the rejection. A summary of the arguments in the reply is provided below with response to arguments following.

A) The reply asserts that Houstek does not provide motivation to screen only nuclear genes but rather in the second paragraph of Houstek states that ATPase subunits include both nuclear and mitochondrial genes (p. 5 last paragraph to p. 61st paragraph). The reply asserts that therefore one would not exclude mitochondrial genes because ATPase defects may result form a mutation in either the mitochondrial or nuclear DNA (p. 6 1st paragraph). The reply points to p. 1969, left column 3rd full paragraph and asserts that the analysis was first performed on mtDNA and that this analysis failed to find deletions and that only then did Houstek test the possibility that the observed

ATPase detected was nuclear (p. 6 1st full paragraph). The reply asserts that Houstek therefore explicitly teaches analysis of both mitochondrial and nuclear DNA (p. 6 1st paragraph).

These arguments have been fully reviewed but have not been found persuasive.

The reply seems to be asserting that because Houstek et al. teaches the analysis of both mitochondrial and nuclear DNA that it does not suggest making a microarray which consists of only nuclear genes of the mitochondrial respiratory chain. However as pointed out by the reply on page1969, left column 3rd full paragraph and asserts that the analysis was first performed on mtDNA and that this analysis failed to find deletions and only the mutations within the nuclear DNA were correlative. Therefore Houstek et al. teaches a particular mutation found only within nuclear genes of the ATPase subunits. As suggested by Houstek this mutation can affect early stage defects caused by nuclear genes. Therefore there is suggestion within Houstek et al. to focus a screening microarray towards the nuclear gene wherein the mutation is found. Although Houstek et al. first screens mitochondrial DNA, the reference teaches that the mutation is within nuclear genes. As such the ordinary artisan would be motivated to screen only the nuclear genes (e.g. an array consisting of probes of nuclear genes) in order to detect such a mutation.

B) The reply asserts that Chee provides no suggestion to analyze only nuclear genes and further teaches that microarray containing mitochondrial DNA would be useful for diagnosis of diseases (p. 6 2nd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

Though there is an example in Chee directed to mitochondrial DNA, Chee teaches the general motivation and design of an array comprising capture probes to interrogate any reference sequence for identification of single base mutants associated with disease (see figure 16 p. 79 lines 23-29, p. 11 lines 9-10, and p. 31 lines 6-7). Herein in the instant case Chee et al. teaches that a microarray can be made consisting of any particular sequence that includes multiple probe sets that represent ever permutation of the nucleotides for a given sequence. In the case of Houstek, the array design of Chee would be used to interrogate the nuclear gene which encompasses a mutations of early stage defect.

C) The reply asserts that Houstek teaches a variety of techniques but does not suggest identifying mutations through the use of a microarray (p. 6 last paragraph). The reply asserts that this deficiency is not remedied by Chee because this reference does not teach analysis of nuclear encoded genes of the mitochondrial respiratory chain using a microarray (p. 7 1st paragraph). The reply asserts that therefore there is nothing in the references to lead the skilled artisan to combine the genes of Houstek with the microarray of Chee (p. 7 1st paragraph).

These arguments have been fully reviewed but have not been found persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Specifically Houstek et al. does not teach using a microarray to screen for the nuclear mutation of ATPase, however, in combination with Chee it does teach this embodiment. Further, although Chee et al. does not specifically teach making an array with nuclear genes, it does teach that any reference target can be used to design an array which has every permutation of the target for genetic mutation screening. Herein in the instant case it would be obvious to take the nuclear gene ATPase as taught by Houstek and make an array to screen for mutations associated with early development.

D) The reply asserts that the claims are amended to wild type nucleic acid molecules and as Chee teaches a substantial number of mutant sequences the microarray of Chee and Houstek would not consist of 90% nucleic acid molecules that are wild type (p. 7 2nd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

It is noted that the interpretation of the claims is broader that a microarray consisting of at least 90% of wild type nucleic acid molecules that encode

polypeptides of Complex I, II, III, IV, or V. Rather the claimed microarray can include fragments of wild type nucleic acid molecules that are at least 15 nucleotides in length. These fragments would include a mutant site (as taught by Chee et al.) but also would encompass a fragment of a wild type nucleic acid. Specifically Chee et al. teaches that only one nucleotide is changed from the reference sequence (e.g. the wild type) for each probe (p. 32 lines 18-19). Therefore the fragment of nucleic acid produced by the design of Chee would encompass a probe comprising a fragment of the wild type nuclear gene (e.g. the nuclear ATPase taught by Houstek et al).

10. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Houstek et al. (Human Molecular Genetics 1999 Vol. 8 p 1967) and Chee et al. (WO 95/11995 May 4, 1995), as applied to 1-2 and 40-41 and in view of Hogan(US Patent 5541308 July 30, 1996).

Houstek et al. and Chee et al. suggest designing a microarray consisting of nucleic acid fragments of the nuclear genes of complex V (e.g. nuclear ATPase genes). However, Houstek et al. and Chee et al. do not teach probes of 40 nucleotides in length.

With regard to Claim 39, Chee et al. teaches that arrays can be designed such that a range of lengths of probes can be employed including probes of at least 30 nucleotides (p. 26 lines 23-25 and p. 27 lines 1-5).

Hogan et al. teaches that probes can be designed which detect target sequences such that the length is at least 40 nucleotides. Hogan et al. provides

guidance for the selection of probes from a known region to detect a target. Hogan teaches that "while oligonucleotide probes of different lengths and base composition may be used, oligonucleotide probes preferred in this invention are between about 15 and about 50 bases in length" (see Column 10, lines 13-15). Therefore Hogan teaches design optimization to design probes that are at least 40 nucleotides in length.

Therefore it would be prima facie obvious to modify the microarray of Houstek and Chee et al. comprising nucleotide probes with the teaching of Hogan et al. to have probes of at least 50 nucleotides in length. Chee et al teaches that a range of lengths of probes can be employed (p. 26 lines 23-25). Therefore it would be considered routine optimization to include probes of at least 40 nucleotides in length. As Hogan teaches that such lengths can be used in hybridization techniques, the length of the probes are known in the art to be used in detection methods. Therefore the ordinary artisan would have a predictable expectation of being able to design a microarray which encompasses probes of at least 40 nucleotides in length that can be used to detect the target.

Response to Arguments

The reply traverses the rejection. A summary of the arguments in the reply is provided below with response to arguments following.

The reply asserts that Houstek and Chee fail to teach the use of microarray to analyze nuclear encoded genes of the mitochondrial respiratory chain (p. 7 last paragraph). The reply asserts that Hogan does not remedy theses deficiencies (p. 8 2nd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

As discussed above, the claims have not been limited to only wild type nucleic encoded genes of the mitochondrial respiratory chain. Rather the claims encompass fragments which would encompass wild type nucleic acids but also would encompass the particular mutational sites discussed in the art rejection.

11. Claims 1 and 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rustin et al. (Biochimica et Biophysica Acta Vol 1553 2002 p. 117) in view of Chee et al. (WO 95/11995 May 4, 1995).

With regard to claim 1, Rustin et al. teaches that complex II of mitochondrial respiratory chain cycle is composed of four subunits all of which are encoded by nuclear DNA (p. 117 1st paragraph). Rustin et al. teaches that defects within this region are relatively rare but are associated with a wide spectrum of clinical phenotypes ranging from encephalomyopahty in childhood to optic atrophy in adulthood (p. 118 1st column 2nd paragraph). Rustin et al. teaches that there are many mutations within complex II which cause various phenotypic defeats (p. 118 2nd column 2nd paragraph and the discussion of particular mutations on p. 118-119). As such Rustin et al. teaches that there are many mutations of the complex II genes which are associated with phenotypic defects. Rustin et al. teaches that complex II only comprise subunits which encompass polypeptides coded for by nuclear genes. Rustin et al. asserts that these nuclear genes of complex II could be involved in structural assembly

defects (p. 121 last paragraph). Rustin et al. teaches mutations in complex II genes could be associated with newly described diseases or of old disease of yet unknown mitochondrial origin (p. 121 last paragraph).

As such, Rustin suggests a use for the detection of mutations within the complex II region. Although Rustin et al. does not teach a microarray consisting of nuclear genes of complex II, the art at the time of filing teaches that it is obvious to place a known region on an array in order to detect mutational differences associated with diseases. Herein in the instant case, Rustin et al. suggests that complex II mutations can be involved with diseases and therefore the ordinary artisan would be motivated to detect mutations within complex II. As complex II only have nuclear genes, microarrays would consist of nuclear genes.

With regard to Claims 1, Chee et al teaches the design of an array comprising capture probes to make a block tiling array (see figure 16, p. 79 lines 23-39 and Figure 7, p. 37 lines 10-38). Chee et al. teaches the design of these tiling arrays to interrogate a reference sequence and its codons with a target sequence for the identification of single base mutants associated with disease (p. 11 lines 9-10 and p. 31 line 6-7). Chee et al. teaches that this design allows for simultaneous detection and quantification of multiple target sites (p. 32 lines 18-19). As such Chee et al. teaches a microarray which consists of a particular sequence that includes multiple probe sets that represent every permutation of the nucleotides for given sequence. Therefore Chee teaches a design which will allow the analysis of all combinations of nucleotides surrounding a region of interest. As such the prior art teaches that once a region of interest is

determined, in this case, the nuclear ATPase subunits, that a microarray comprising every permutation of that region can be designed for the purpose of identifying mutations associated with disease.

With regard to Claims 40-41, the array designed by Chee et al. would include every permutation of the target sequences of the nuclear ATP synthase of Houstek et al. and therefore would encompass at least 25 nucleic acid molecules.

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time of filing to design a microarray consisting of complex II genes (e.g. consisting of nuclear genes) using the design constraints of Chee et al. Rustin et al. suggests that mutations within complex II genes can be associated with a number of phenotypic defects. The artisan thus would have been motivated to detect mutations within the complex II genes that may affect function of the genes during development. Chee et al. teaches that the design of such microarrays to screen such mutations in simultaneous fashion was known in the art. As such the ordinary artisan would have a reasonable expectation of success of designing a microarray consisting of nucleic acid probes of complex II for the expressed purpose of screening for diseases.

Response to Arguments

The reply traverses the rejection. A summary of the arguments in the reply is provided below with response to arguments following.

A). The reply asserts that there is no basis for studying complex II genes with a microarray, but rather the references cited by Rustin are directed towards

direct sequencing (p. 8 last paragraph). The reply asserts that Chee fails to overcome the deficiency because Chee does not provide a suggestion of making a nuclear gene microarray but rather teaches that microarrays containing mitochondrial DNA would be valuable (p. 9 1st paragraph).

These arguments have been fully reviewed but have not been found persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Specifically Rustin et al. does not teach using a microarray to screen for the nuclear DNA of complex II of the mitochondrial respiratory chain cycle, however, in combination with Chee it does teach this embodiment. Further, although Chee et al. does not specifically teach making an array with nuclear genes, it does teach that any reference target can be used to design an array which has every permutation of the target for genetic mutation screening. Herein in the instant case it would be obvious to nuclear genes of Complex II as taught by Rustin and make an array to screen for mutations associated with disease as taught in the design parameters of Chee et al.

Though there is an example in Chee directed to mitochondrial DNA, Chee teaches the general motivation and design of an array comprising capture probes to interrogate any reference sequence for identification of single base mutants associated with disease (see figure 16 p. 79 lines 23-29, p. 11 lines 9-10, and p.

31 lines 6-7). Herein in the instant case Chee et al. teaches that a microarray can be made consisting of any particular sequence that includes multiple probe sets that represent ever permutation of the nucleotides for a given sequence. In the case of Rustin, the array design of Chee would be used to interrogate ATP complex II genes for mutations associated with disease (p. 121 last paragraph of Rustin et al.).

B). The reply asserts that further claim 1 has been amended to recite wild type nucleic acids molecules which is not taught by the combination of Rustin and Chee (p. 9 2nd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

It is noted that the interpretation of the claims is broader that a microarray consisting of at least 90% of wild type nucleic acid molecules that encode polypeptides of Complex I, II, III, IV, or V. Rather the claimed microarray can include fragments of wild type nucleic acid molecules that are at least 15 nucleotides in length. These fragments would include a mutant site (as taught by Chee et al.) but also would encompass a fragment of a wild type nucleic acid. Specifically Chee et al. teaches that only one nucleotide is changed from the reference sequence (e.g. the wild type) for each probe (p. 32 lines 18-19). Therefore the fragment of nucleic acid produced by the design of Chee would encompass a probe comprising a fragment of the wild type nuclear gene (e.g. the nuclear ATPase taught by Houstek et al).

12. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rustin et al. (Biochimica et Biophysica Acta Vol 1553 2002 p. 117) and Chee et al. (WO 95/11995 May 4, 1995), as applied to 1-2 and 40-41 and in view of Hogan(US Patent 5541308 July 30, 1996).

Rustin et al. and Chee et al. suggest designing a microarray consisting of nucleic acid fragments of the nuclear genes of complex II (e.g. nuclear genes). However, Rustin et al. and Chee et al. do not teach probes of 40 nucleotides in length.

With regard to Claim 39, Chee et al. teaches that arrays can be designed such that a range of lengths of probes can be employed including probes of at least 30 nucleotides (p. 26 lines 23-25 and p. 27 lines 1-5).

Hogan et al. teaches that probes can be designed which detect target sequences such that the length is at least 40 nucleotides. Hogan et al. provides guidance for the selection of probes from a known region to detect a target. Hogan teaches that "while oligonucleotide probes of different lengths and base composition may be used, oligonucleotide probes preferred in this invention are between about 15 and about 50 bases in length" (see Column 10, lines 13-15). Therefore Hogan teaches design optimization to design probes that are at least 40 nucleotides in length.

Therefore it would be prima facie obvious to modify the microarray of Rustin and Chee et al. comprising nucleotide probes with the teaching of Hogan et al. to have probes of at least 50 nucleotides in length. Chee et al teaches that a

range of lengths of probes can be employed (p. 26 lines 23-25). Therefore it would be considered routine optimization to include probes of at least 40 nucleotides in length. As Hogan teaches that such lengths can be used in hybridization techniques, the length of the probes are known in the art to be used in detection methods. Therefore the ordinary artisan would have a predictable expectation of being able to design a microarray which encompasses probes of at least 40 nucleotides in length that can be used to detect the target.

Response to Arguments

The reply traverses the rejection. A summary of the arguments in the reply is provided below with response to arguments following.

The reply asserts that Rustin and Chee fail to teach the use of microarray to analyze wild type nuclear encoded genes of the mitochondrial respiratory chain (p. 10 1st two paragraphs). The reply asserts that Hogan does not remedy theses deficiencies (p. 10 1st two paragraphs).

These arguments have been fully reviewed but have not been found persuasive.

As discussed above, the claims have not been limited to only wild type nucleic encoded genes of the mitochondrial respiratory chain. Rather the claims encompass fragments which would encompass wild type nucleic acids but also would encompass the particular mutational sites discussed in the art rejection.

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday - Friday 9AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Katherine Salmon/
Examiner, Art Unit 1634